Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-250 Olaparib

Stand: September 2020

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Olaparib
[in Kombination mit Bevacizumab zur Erhaltungstherapie des epithelialen Ovarialkarzinoms, Eileiterkarzinoms oder primären Peritonealkarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“* • Arzneimittel für die Erhaltungstherapie von Patientinnen mit einem Platin-sensitiven Rezidiv wurden nicht berücksichtigt. • Arzneimittel mit expliziter Zulassung für die Zweit- bzw. Folgelinientherapie wurden nicht berücksichtigt.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	Nicht angezeigt.
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Olaparib L01XX46 Lynparza®	**Anwendungsgebiet:** Lynparza in Kombination mit Bevacizumab wird angewendet für die: Erhaltungstherapie von erwachsenen Patientinnen mit einem fortgeschrittenen (FIGO-Stadien III und IV) high-grade epithelialen Ovarialkarzinom, Eileiterkarzinom oder primären Peritonealkarzinom, die nach einer abgeschlossenen Platin-basierten Erstlinien-Chemotherapie in Kombination mit Bevacizumab ein Ansprechen (vollständig oder partiell) haben und deren Tumor mit einem positiven Status der homologen Rekombinations-Defizienz (HRD) assoziiert ist. Der Status HRD-positiv ist definiert entweder durch eine BRCA1/2-Mutation und/oder genomische Instabilität.
Bevacizumab L01XC07 Avastin®	Bevacizumab wird in Kombination mit Carboplatin und Paclitaxel zur Primärbehandlung von erwachsenen Patienten mit fortgeschrittenem epitelialem Ovarialkarzinom, Eileiterkarzinom oder primärem Peritonealkarzinom in den International Federation of Gynecology and Obstetrics (FIGO)-Stadien IIIB, IIIC und IV angewendet. […] 4.2 Dosierung und Art der Anwendung Epitheliales Ovarialkarzinom, Eileiterkarzinom und primäres Peritonealkarzinom Primärbehandlung: Avastin wird über bis zu 6 Behandlungszyklen zusätzlich zu Carboplatin und Paclitaxel und in der Folge als Monotherapie bis zum Fortschreiten der Erkrankung oder bis zu einem maximalen Zeitraum von 15 Monaten oder bis zum Auftreten nicht mehr tolerierbarer Nebenwirkungen, je nachdem was früher eintritt, angewendet. Die empfohlene Avastin Dosis beträgt 15 mg/kg Körpergewicht einmal alle 3 Wochen als intravenöse Infusion.
Olaparib L01XX46 Lynparza®	Lynparza wird angewendet als Monotherapie für die: • Erhaltungstherapie von erwachsenen Patientinnen mit einem fortgeschrittenen (FIGO-Stadien III und IV) BRCA1/2-mutierten (in der Keimbahn und/oder somatisch), high-grade epithelialen Ovarialkarzinom, Eileiterkarzinom oder primären Peritonealkarzinom, die nach einer abgeschlossenen Platin-basierten Erstlinien-Chemotherapie ein Ansprechen (vollständig oder partiell) haben. […]
Carboplatin L01XA02 generisch	CARBO-cell® ist allein oder in Kombination mit anderen antineoplastisch wirksamen Medikamenten bei der Behandlung folgender maligner Geschwülste angezeigt: - epitheliale Ovarialkarzinome

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	- […]
Cisplatin L01XA01 generisch	Cisplatin Teva® wird angewendet zur Behandlung des: - fortgeschrittenen oder metastasierten Ovarialkarzinoms - […]
Cyclophosphamid L01AA01 generisch	Cyclophosphamid ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: - fortgeschrittenes Ovarialkarzinom
Doxorubicin L01DB01 generisch	- fortgeschrittenes Ovarialkarzinom - […]
Epirubicin L01DB03 generisch	Epirubicin ist für die Behandlung folgender maligner Erkrankungen in Mono- und Kombinationsschemata angezeigt: - fortgeschrittenes Ovarialkarzinom - […]
Paclitaxel L01CD01 generisch	Ovarialkarzinom Zur First-line Chemotherapie von Eierstockkrebs ist Paclitaxel HAEMATO 6 mg/ml bei Patientinnen mit fortgeschrittenem Eierstockkrebs oder einem Resttumor (>1 cm) nach vorausgegangener Laparotomie in Kombination mit Cisplatin indiziert. […]
Treosulfan L01AB02 Ovastat	Ovastat 1000 (5000) mg ist allein oder in Kombination mit anderen antineoplastisch wirksamen Substanzen angezeigt in der palliativen Therapie epithelialer Ovarialkarzinome der FIGO Stadien II – IV. Eine Therapie mit Treosulfan allein (Monotherapie) ist angezeigt, wenn eine Kontraindikation gegen Cisplatin besteht. In allen anderen Fällen sollte Treosulfan mit Cisplatin kombiniert werden.
Melphalan 01AA03 generisch	Melphalan-ratiopharm® wird in der konventionellen intravenösen Dosierung zur Behandlung des multiplen Myeloms und des Ovarialkarzinoms angewendet. […] Melphalan-ratiopharm® kann in den oben genannten Anwendungsgebieten allein oder in Kombination mit anderen Zytostatika angewendet werden.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2019-B-250 (Olaparib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. November 2019

Inhaltsverzeichnis

Abkürzungsverzeichnis

AOC	Advanced ovarian cancer
AEOC	Advanced epithelial ovarian cancer
ASCO	American Society of Clinical Oncology
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
EOC	Epithelial ovarian cancer
ESMO	European Society for Medical Oncology
ESGO	European Society of Gynaecologial Oncology
FIGO	International Federation of Gynecologists and Obstetricians
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HIPEC	Hypertherme intraperitoneale Chemotherapie
HR	Hazard Ratio
ICS	Interval cytoreductive surgery
IDS	Interval debulking surgery
IP	Intra-peritoneal
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NAC	Neoadjuvant chemotherapy
NACT-IDS	Neoadjuvant chemotherapy followed by interval debulking surgery
NICE	National Institute for Health and Care Excellence
OC	Ovarian cancer
OR	Odds Ratio
ORR	Objective response rate
OS	Overall survival
PC	Paclitaxel+carboplatin
PCS	Primary cytoreductive surgery

PLD	pegylated liposomal doxorubicin
PDS	Primary debuling surgery
PFS	Progression free survival
QoL	Quality of life
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SGO	Society of Gynecologic Oncology
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Anwendungsgebiet:

Lynparza in Kombination mit Bevacizumab wird angewendet für die:

Erhaltungstherapie von erwachsenen Patientinnen mit einem fortgeschrittenen (FIGO-Stadien III und IV) high-grade epithelialen Ovarialkarzinom, Eileiterkarzinom oder primären Peritonealkarzinom, die nach einer abgeschlossenen Platin-basierten Erstlinien-Chemotherapie in Kombination mit Bevacizumab ein Ansprechen (vollständig oder partiell) haben und deren Tumor mit einem positiven Status der homologen Rekombinations-Defizienz (HRD) assoziiert ist. Der Status HRD-positiv ist definiert entweder durch eine BRCA1/2-Mutation und/oder genomische Instabilität.

Indikation für die Synopse:

Behandlung des fortgeschrittenen Ovarial-, Eileiter- oder primären Peritonealkarzinoms.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zu den Indikationen *Ovarialkarzinom, Eileiterkarzinom und primäres Peritonealkarzinom* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 18.01.2019 durchgeführt, die Folgerecherchen am 02.05.2019 und 16.10.2019. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

Die Recherchen ergaben insgesamt 1722 Quellen, die in einem zweistufigen Screening-Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Es wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen und nur die Quellen der letzten 5 Jahre berücksichtigt. 17 Quellen wurden in die synoptische Evidenz-Übersicht aufgenommen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es konnten relevanten G-BA Beschlüsse/IQWIG-Berichte identifiziert werden.

3.2 Cochrane Reviews

Tangjitgamol S et al., 2016 [12].

Interval debulking surgery for advanced epithelial ovarian cancer

Fragestellung

To assess the effectiveness and complications of interval debulking surgery (IDS) for women with advanced stage epithelial ovarian cancer.

Methodik

Population:

- Women with advanced stage epithelial ovarian cancer who have a confirmed pathological diagnosis from primary surgery which was suboptimal, with residual tumours of more than 1 to 2 cms.

Intervention:

- Interval debulking surgery (IDS), defined as secondary surgery which is performed after two to four cycles of neoadjuvant chemotherapy (NAC)

Komparator:

- Adjuvant chemotherapy only.

Endpunkte:

- OS, PFS, adverse events, QoL

Recherche/Suchzeitraum:

- Central, Medline 2015

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

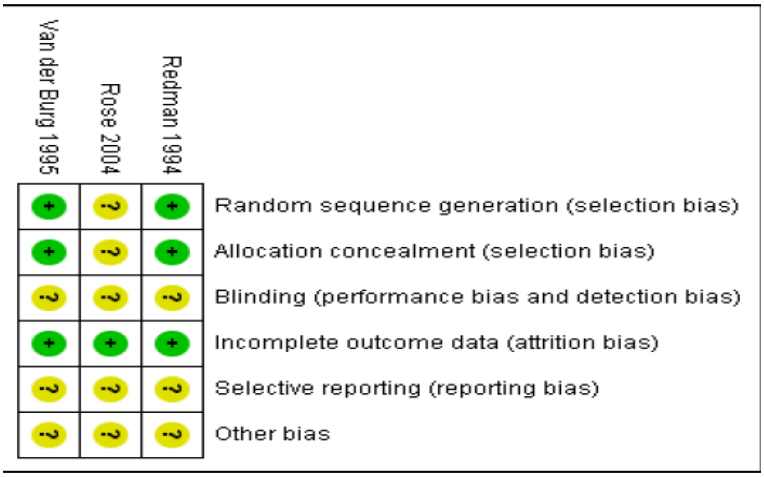
- 3 RCTs

Charakteristika der Population:

- Median length of follow-up was reported in all three trials: 48 months (Redman 1994), 42 months (Van der Burg 1995), and.47 months (Rose 2004). Although Van de Burg and colleagues from the EORTC presented their long-term follow-up (10 years) as an oral presentation in the European Society of Gynaecological Oncology annual meeting in 2005 (Van der Burg 2005), the data were insufficient to include in our meta-analysis.
- Redman 1994: IDS: after 1 - 4 cycles of induction chemotherapy consisting of IV cisplatin 75 mg/ m² + cyclophosphamide 750 mg/m² or cisplatin 75 mg/m² + doxorubicin 50 mg/m² +bleomycin 50 mg/m² followed by escalated dose of cyclophosphamide (0.5 g/m²-2.5 g/m²) up to 5 cycles. Chemotherapy cycles were repeated every 3 weeks.

- Rose 2004: IDS: after 3 cycles of chemotherapy consisting of IV paclitaxel 135 mg/m² + cisplatin 75 mg/m² every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS.
- Van der Burg 1995: IDS: after 3 cycles of induction chemotherapy composing of IV cyclophosphamide 750 mg/m² + IV cisplatin 75 mg/m² every 3 weeks. Three more cycles of the same chemotherapy regimen were given after IDS.

Qualität der Studien:



Studienergebnisse:

OS

- Meta-analysis of two trials (Redman 1994; Van der Burg 1995) assessing 357 women who received surgery from a general surgeon found that IDS with chemotherapy was associated with a statistically significant decrease in the risk of death compared with chemotherapy alone (HR = 0.68, 95% CI 0.53 to 0.87, I^2 = 0%).
- Rose 2004, assessing 424 participants, found no statistically significant difference in the risk of death between IDS with chemotherapy and chemotherapy alone (HR = 0.99, 95% CI 0.79 to 1.24.

Quality of life (QoL)

- Only Rose 2004 evaluated QoL, which was subsequently reported by Wenzel 2005. At six months after starting treatment, significantly more women who had only chemotherapy experienced persistent numbness or tingling than those who had IDS (54%versus 38%; P = 0.01). Otherwise, QoL was not significantly different in the two treatment groups at any time point.

Adverse events

- Toxic reactions to chemotherapy: Meta-analysis of two trials (Redman 1994; Van der Burg 1995), assessing 357 participants, found no statistically significant difference in the risk of disease progression between IDS with chemotherapy and chemotherapy alone (HR = 1.19, 95% CI 0.53 to 2.66; I2: 0%)

Anmerkung/Fazit der Autoren

The heterogeneity of the results in our review precludes any definitive guidance or recommendations for clinical practice. Without strong evidence to support the superiority of interval debulking surgery (IDS) in combination with chemotherapy over conventional primary surgery and chemotherapy, a clinician may remain unconvinced of the benefit of IDS instead of aggressive primary surgery for a woman with advanced ovarian cancer. The choice of extensive primary surgery or upfront chemotherapy followed by IDS must be individualized to each patient. Since we found a benefit of IDS in the subgroup of women whose primary surgery had not been performed under optimal conditions by the oncologic surgeons or without maximum surgical effort, we suggest that IDS may improve patient survival in this setting.

3.3 Systematische Reviews

Qu CP et al., 2017 [8].

Toxicities of different first-line chemotherapy regimens in the treatment of advanced ovarian cancer: a network meta-analysis

Fragestellung

Ovarian cancer (OC) is the 5th leading cause of cancer-related deaths around the world, and several chemotherapy regimens have been applied in the treatment of OC. We aim to compare toxicities of different chemotherapy regimens in the treatment of advanced ovarian cancer (AOC) using network meta-analysis.

Methodik

Population:

- patients with advanced ovarial cancer (AOC) aged 19 to 84 years

Intervention und Komparator:

- paclitaxel+carboplatin (PC), pegylated liposomal doxorubicin (PLD) +Carboplatin, Carboplatin, Gemcitabine +Carboplatin, Paclitaxel, PC+Epirubicin, PC+Topotecan and Docetaxel+Carboplatin

Endpunkt:

- anemia, febrile neutropenia, thrombocytopenia, nausea, vomiting, fatigue, and diarrhea

Recherche/Suchzeitraum:

- Cochrane Library, PubMed, and EMBASE was performed up to November 2015

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

Eventually, 13 eligible RCTs,[21–33] published between 2004 and 2015, were included for this network metaanalysis (n= 7841 patients)

Charakteristika der Population:

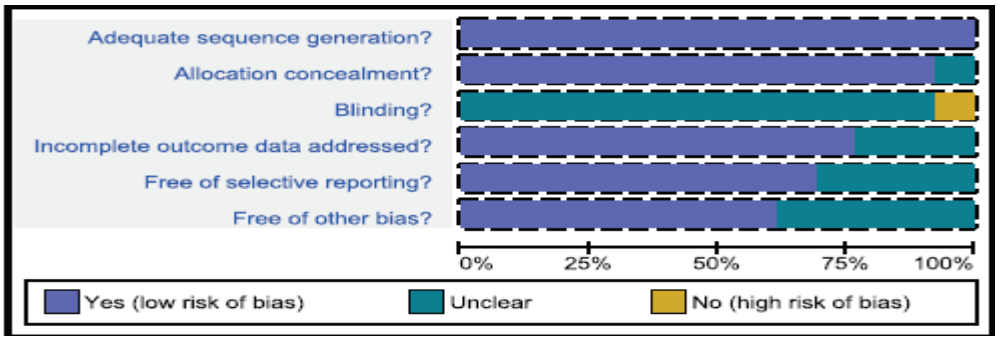
Table 1

The baseline characteristics for included studies.

First author	Year	Country	Interventions T1	Interventions T2	Total	Number T1	Number T2	Age (y) T1	Age (y) T2
Mahner et al	2015	Germany	A	B	259	128	131	63 (27–82)	60 (30–80)
Lortholary et al	2012	France	A	E	108	51	57	60 (43–77)	60 (30–80)
Lindemann et al	2012	Norway	A	F	887	442	445	80 (25–80)	57 (28–79)
Gladieff et al	2012	France	A	B	344	183	161	60 (30–80)	60 (24–82)
Gordon et al	2011	USA	A	D	831	414	417	60 (22–86)	60 (22–84)
Pujade-Lauraine et al	2010	France	A	B	973	507	466	61 (27–82)	65 (24–82)
Bolis et al	2010	Italy	A	G	326	170	156	57.4 ± 10.2	58.7 ± 9.4
Alberts et al	2008	USA	B	C	61	31	30	66.9 (43–87)	62.5 (31–80)
Mori et al	2007	Japan	A	H	29	16	13	54.9	57.7
Pfisterer et al	2006	Germany	A	G	1308	650	658	60 (20–81)	60 (20 – 81)
du Bois et al	2006	Germany	A	F	1282	635	647	58 (22–79)	60 (21–79)
Pfisterer et al	2005	Germany	D	C	356	178	178	56.5 (21–81)	58.1 (36–78)
Vasey et al	2004	UK	A	H	1077	538	539	59 (19–84)	59 (21–85)

Abkürzungen: A=paclitaxel+carboplatin, B=pegylated liposomal doxorubicin+carboplatin, C=carboplatin, D=gemcitabine+carboplatin, E=paclitaxel, F=paclitaxel+carboplatin+Epirubicin, G=paclitaxel+carboplatin +topotecan, H=docetaxel+carboplatin, T=treatment.

Qualität der Studien:



Studienergebnisse

SUCRA values of 11 treatment modalities under 6 endpoint outcomes.

Treatments	SUCRA values						
	Anaemia	Febrile neutropenia	Thrombocytopenia	Nausea	Diarrhea	Vomiting	Fatigue
A	0.621	0.554	0.649	0.660	0.646	0.595	0.579
B	0.409	0.639	0.356	0.381	0.846	**0.300**	0.687
C	0.761	0.691	0.799	0.957	NA	0.405	0.520
D	**0.220**	**0.170**	**0.196**	0.604	NA	0.605	**0.383**
E	0.924	0.784	0.834	NA	NA	0.615	0.623
F	NA	0.276	NA	**0.231**	0.488	0.509	NA
G	0.349	0.880	0.471	0.767	0.730	0.743	0.621
H	0.770	NA	0.696	0.380	**0.292**	0.711	0.586

Abkürzungen: A=paclitaxel+carboplatin, B=pegylated liposomal doxorubicin+carboplatin, C=carboplatin, D=gemcitabine+carboplatin, E=paclitaxel, F=paclitaxel+carboplatin+Epirubicin, G=paclitaxel+carboplatin +topotecan, H=docetaxel+carboplatin, T=treatment.

- Pairwise meta-analysis and network meta-analysis results showed that the toxicity of PC chemotherapy regimen was lower than that of the other 7 chemotherapy regimens.

- Generally, the incidence hematologic toxicity of gemcitabine+carboplatin regimen was highest for AOC patients, and PC+epirubicin, PLD+carboplatin, and docetaxel+carboplatin regimens had higher incidence of non-hematologic toxicity for AOC patients.
  - The lowest SUCRA value of the incidence of fatigue (38.3%), anemia (22.0%), febrile neutropenia (17.0%), and thrombocytopenia (19.6%) was gemcitabine+carboplatin chemotherapy regimen. Besides, the PC+epirubicin chemotherapy regimen achieved the lowest SUCRA value of the incidence of nausea (23.1%). However, the PLD+carboplatin regimen showed lower SUCRA value of vomiting (30.0%) and the docetaxel+carboplatin regimen had lower SUCRA value of diarrhea (29.2%) than other regimens.
  - Generally, the incidence of hematologic toxicity of gemcitabine+carboplatin regimen was highest for AOC patients, and PC+epirubicin, PLD+carboplatin and docetaxel+carboplatin regimens had higher incidence of nonhematologic toxicity for AOC patients.

[22] Lortholary A, Largillier R, Weber B, et al. Weekly paclitaxel as a single agent or in combination with carboplatin or weekly topotecan in patients with resistant ovarian cancer: the CARTAXHY randomized phase II trial from Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens (GINECO). Ann Oncol 2012;23:346–52.
[23] Lindemann K, Christensen RD, Vergote I, et al. First-line treatment of advanced ovarian cancer with paclitaxel/carboplatin with or without epirubicin (TEC versus TC)—a gynecologic cancer intergroup study of the NSGO, EORTC GCG and NCIC CTG. Ann Oncol 2012;23:2613–9.
[24] DiarrheaGladieff L, Ferrero A, De Rauglaudre G, et al. Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in partially platinum-sensitive ovarian cancer patients: results from a subset analysis of the CALYPSO phase III trial. Ann Oncol 2012;23:1185–9.
[25] Gordon AN, Teneriello M, Janicek MF, et al. Phase III trial of induction gemcitabine or paclitaxel plus carboplatin followed by paclitaxel consolidation in ovarian cancer. Gynecol Oncol 2011;123:479–85.
[26] Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, et al. Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol 2010;28:3323–9.
[27] Bolis G, Scarfone G, Raspagliesi F, et al. Paclitaxel/carboplatin vers topotecan/paclitaxel/carboplatin in patients with FIGO suboptimally resected stage III–IV epithelial ovarian cancer a multicenter, randomize study. Eur J Cancer 2010;46:2905–12.
[28] Alberts DS, Liu PY, Wilczynski SP, et al. Randomized trial of pegylated liposomal doxorubicin (PLD) plus carboplatin versus carboplatin in platinum-sensitive (PS) patients with recurrent epithelial ovarian or peritoneal carcinoma after failure of initial platinum-based chemotherapy (Southwest Oncology Group Protocol S0200). Gynecol Oncol 2008;108:90–4.
[29] Mori T, Hosokawa K, Kinoshita Y, et al. A pilot study of docetaxel carboplatin versus paclitaxel-carboplatin in Japanese patients with epithelial ovarian cancer. Int J Clin Oncol 2007;12:205–11.
[30] Pfisterer J, Weber B, Reuss A, et al. Randomized phase III trial of topotecan following carboplatin and paclitaxel in first-line treatment of advanced ovarian cancer: a gynecologic cancer intergroup trial of the AGO-OVAR and GINECO. J Natl Cancer Inst 2006;98:1036–45.
[31] du Bois A, Weber B, Rochon J, et al. Addition of epirubicin as a third drug to carboplatin-paclitaxel in first-line treatment of advanced ovarian cancer: a prospectively randomized gynecologic cancer intergroup trial by the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group and the Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens. J Clin Oncol 2006;24:1127–35.
[32] Pfisterer J, Vergote I, Du Bois A, et al. Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer. Int J Gynecol Cancer 2005;15(suppl 1):36–41.
[33] Vasey PA, Jayson GC, Gordon A, et al. Phase III randomized trial of docetaxel-carboplatin versus paclitaxel-carboplatin as first-line chemotherapy for ovarian carcinoma. J Natl Cancer Inst 2004;96: 1682–91.

Anmerkung/Fazit der Autoren

In conclusion, this study clearly demonstrated that the PLD+ carboplatin chemotherapy regimen exerts the highest toxic effects in hematologic on patients with AOC, and it is clinically significant for the future clinical medication and therapy development.

Zeng LJ et al., 2016 [17]. + **Yang L et al., 2017 [16] + Qin M et al., 2018 [7].**

Fragestellung

We aimed to systematically evaluate the influence of neoadjuvant chemotherapy (NAC) on survival and complete cytoreduction after debulking surgery in advanced epithelial ovarian cancer (AEOC) patients.

Methodik

Population:

subjects were patients whose pathological diagnosis was AEOC, with FIGO stage IIB-IV

Intervention + Komparator:

interventions were platinum-based NAC followed by IDS and chemotherapy OR PDS followed by NAC then IDS followed by chemotherapy, compared with PDS followed by platinum-based chemotherapy

Endpunkt:

overall survival (OS), progression-free survival (PFS), no residual disease, residual disease ≤1 cm, and optimal cytoreduction rate. The definition of optimal cytoreductive surgery is residual tumor diameter ≤1 cm or no residual disease after debulking surgery.

Recherche/Suchzeitraum:

PubMed, Embase, and the Cochrane Central Register of Controlled Trials databases were comprehensively and systematically searched from inception to February 25, 2016 without language restrictions.

Qualitätsbewertung der Studien:

Cochrane Collaboration's risk of bias tool

Heterogenitätsmaß:

I^2 (When I2 ≤ 25%, fixed effects model was presented)

Ergebnisse

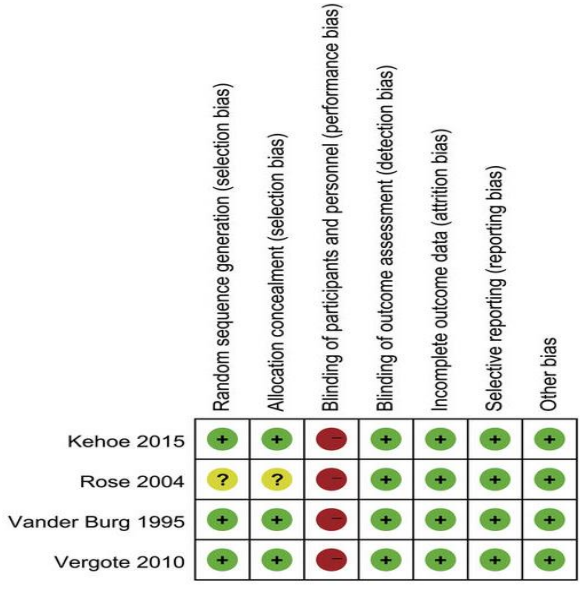
Anzahl eingeschlossener Studien:

- only 4 RCTs containing 1922 patients were included in the meta-analysis process[1,2,4,5]

Charakteristika der Population:

	Sample Size (Exp/Con)	Age (yr)[a]		Follow-up Time	FIGO Stage N (%)		Histopathologic Type,(Exp/Con)	Histologic Grade		Intervention	
		Exp	Con		Exp	Con		Exp	Con	Exp	Con
Kehoe *et al.*[1]	276/274	66	65		III:	III:	Serous 185/219	G1:13	G1:12	NAC × 3 cycles + IDS + Chemotherapy × 3cycles	PDS + chemotherapy × 6cycles
		(26–87)	(34–88)		206 (75.2%)	206 (74.5%)	Mucous 4/2	G2:43	G2:27		
					IV:	IV:	Clear cell 13/4	G3:165	G3:149		
					68 (24.8%)	70 (25.5%)	Endometrioid 5/11				
							Mixed 0/2				
							Unclasstfied 3/12				
Vergote *et al.*[2]	336/334	62	63		IIIC:	IIIC:	Serous 194/220	G1:14	G1:10	NAC × 3 cycles + IDS + Chemotherapy × 3cycles	PDS + chemotherapy × 6cycles
		(25–86)	(33–81)		253 (75.7%)	257 (76.5%)	Mucous 11/8	G2:57	G2:41		
					IV:	IV:	Clear cell 4/6	G3:145	G3:130		
					81 (24.3%)	77 (22.9%)	Endometrioid 5/11	Gx:120	Gx:153		
					other:	other:	Undifferentiated 90/69				
					0	2 (0.6%)	Mixed 0/9				
							Other/Unkoown 30/19				
Rose *et al.*[4]	208/216	57	58.1		III:	III:	Serous 165/159	G1:21	G1:19	PDS + NAC × 3 cycles + IDS + chemotherapy × 3cycles	PDS + chemotherapy × 6cycles
		(27.0–81.6)	(25.4–81.6)		200 (92.6%)	200 (96.2%)	Mucous 1/2	G2:82	G2:85		
					IV:	IV:	Clear cell 4/3	G3:105	G3:112		
					16 (7.4%)	8 (3.8%)	Endometrioid 17/11				
							Mixed 20/17				
							Undifferentiated/ Other 5/8				
							Unspecified 4/8				
Van Der Burg *et al.*[5]	138/140	59	59		IIb:	IIb:	Serous 59/56	G1:9	G1:8	PDS + NAC × 3 cycles + IDS + chemotherapy × 3cycles	PDS + chemotherapy × 6cycles
		(32–74)	(32–74)		4 (4.1%)	4 (4.0%)	Mucous 8/4	G2:32	G2:27		
					III:	III:	Clear cell 1/4	G3:54	G3:61		
					71 (72.5%)	75 (75.0%)	Endometrioid 7/10	Gx:5	Gx:4		
					IV:	IV:	Mixed 0/0				
					23 (23.4%)	21 (21.0%)	Unclasstfied 25/26				

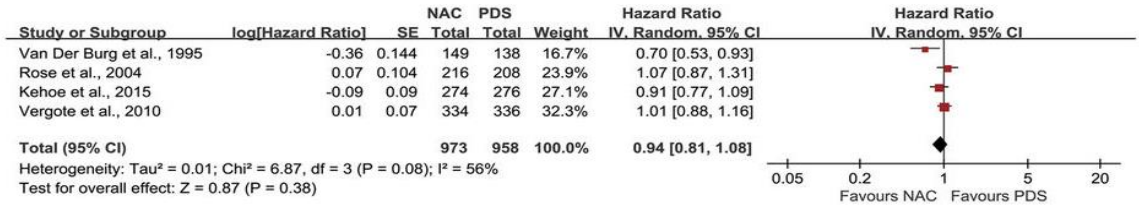
Qualität der Studien:



Studienergebnisse:

Overall survival

From: Neoadjuvant chemotherapy for Patients with advanced epithelial ovarian cancer: A Meta-Analysis



NAC, neoadjuvant chemotherapy followed by interval debulking surgery; PDS, primary cytoreductive surgery followed by systemic chemotherapy.

- From the sensitivity analysis, we found that Van der Burg et al.5 probably contributed to the heterogeneity. After excluding this study, the result suggested that OS of AEOC patients was still similar between NAC and PDS (HR 0.99, 95%CI: 0.90–1.09, P = 0.90), with low heterogeneity (I2 = 0%).

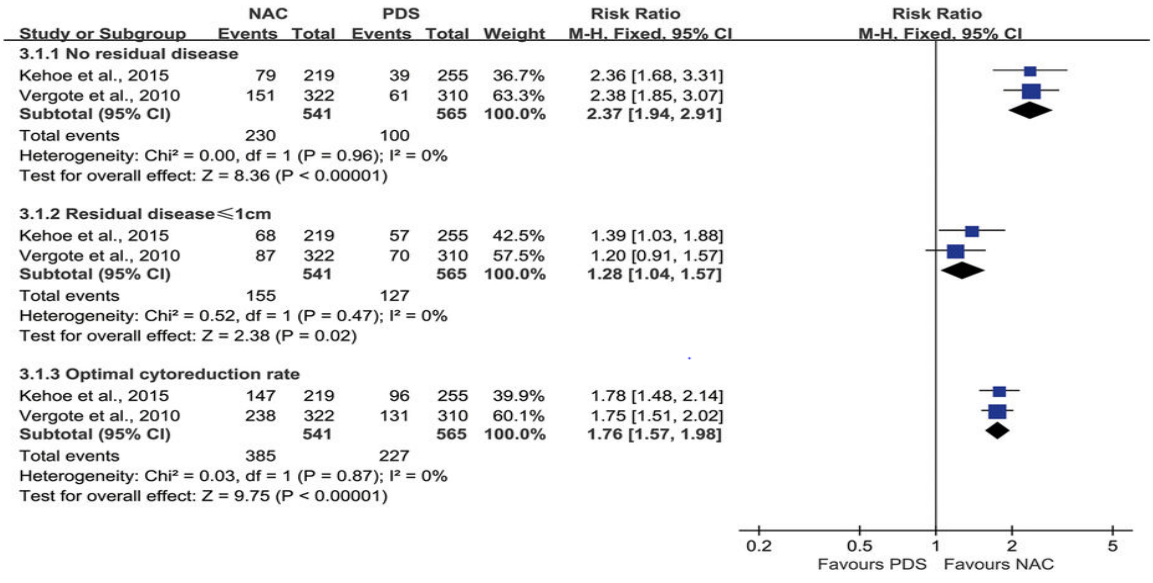
Progression-free survival.

From: Neoadjuvant chemotherapy for Patients with advanced epithelial ovarian cancer: A Meta-Analysis

NAC, neoadjuvant chemotherapy followed by interval debulking surgery; PDS, primary cytoreductive surgery followed by systemic chemotherapy.

Extent of surgical debulking

From: Neoadjuvant chemotherapy for Patients with advanced epithelial ovarian cancer: A Meta-Analysis



1. Kehoe, S. et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an openlabel, randomised, controlled, non-inferiority trial. Lancet. 386, 249–257 (2015).
2. Vergote, I. et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N. Engl. J. Med. 363, 943–953 (2010).
4. Rose, P. G. et al. Secondary surgical cytoreduction for advanced ovarian carcinoma. N. Engl. J. Med. 351, 2489–2497 (2004).
5. van der Burg, M. E. et al. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl. J. Med. 332, 629–634 (1995).

Anmerkung/Fazit der Autoren

In summary, NAC is a reasonable treatment option for FIGO stage III and IV epithelial ovarian cancer patients with non-inferior survival compared with PDS. Furthermore emerging evidences suggests that NAC may be associated with improved QoL compared to PDS. Maximum surgical efforts and improvement of competent surgical skills are necessary, regardless of whether NAC is performed.

Wu S et al., 2017 [15], + Ruan G et al., 2018 [9]. + Li J et al., 2015 [4], Li X et al., 2016 [5], Miao H et al., 2017 [6], Staropoli N et al., 2016 [11], Wang H et al., 2018 [13].

Bevacizumab combined with chemotherapy for ovarian cancer: an updated systematic review and meta-analysis of randomized controlled trials

Fragestellung

This meta-analysis was updated with results from a new trial and final data to reassess the efficacy and safety of bevacizumab combined with chemotherapy in ovarian cancer (OC).

Methodik

Population:

- women with ovarian cancer

Intervention:

- chemotherapy plus bevacizumab

Komparator:

- chemotherapy alone

Endpunkte:

- efficacy and safety

Recherche/Suchzeitraum:

- May 2016: PubMed, EMBASE, Web of Science and Central

Qualitätsbewertung der Studien:

- Cochrane Collaboration’s Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

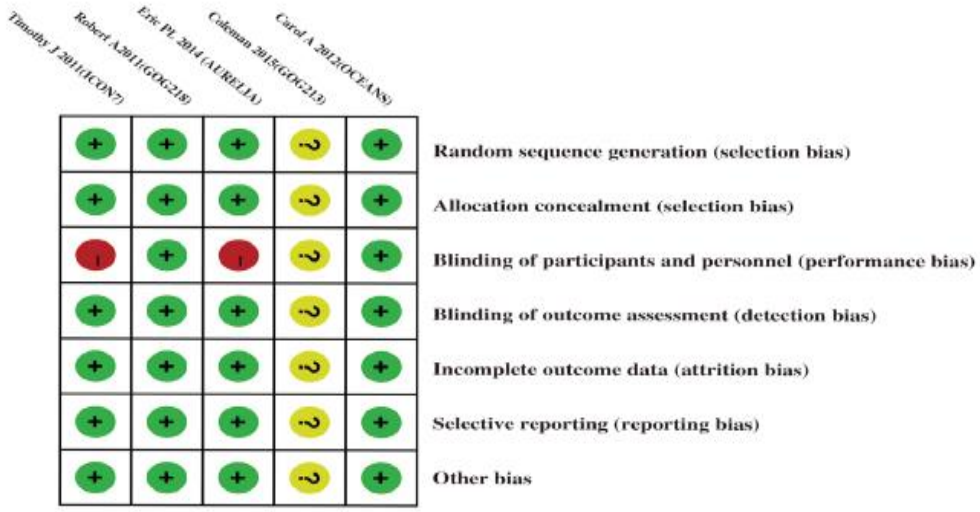
- 5 RCTs (N=4994 Patienten)

Charakteristika der Population:

- 3 Studien zu Recurrent und **2 Studien zu First-Line**
- Relevant im vorliegenden AWG = Studie GOG-0218 (Robert A. Burger et al. 2011) und ICON7 (Timothy J. Perren et al. 2011)

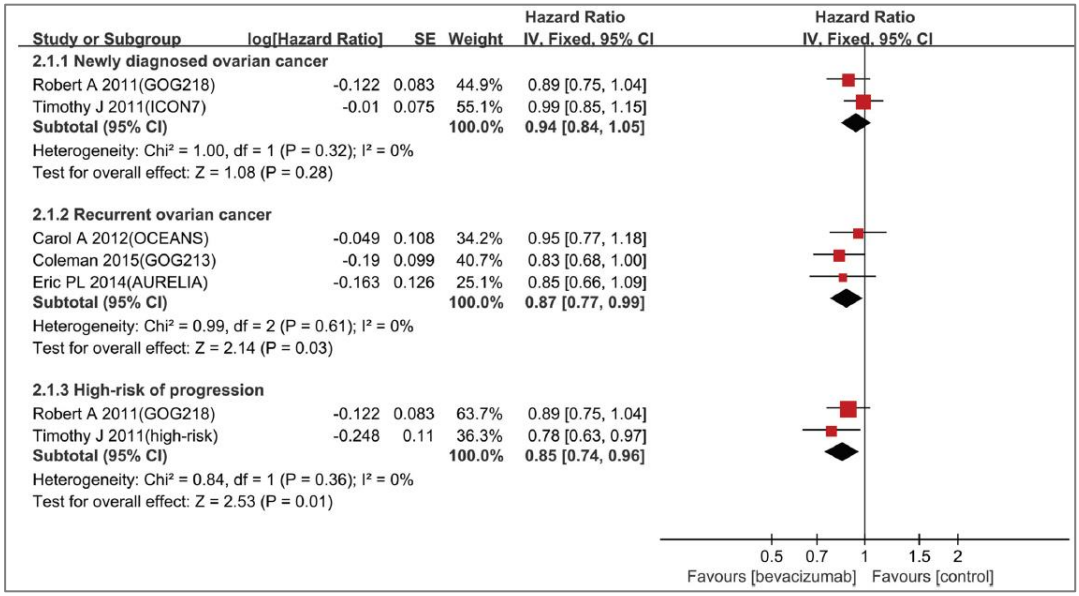
References	Arms	Sample Size	Patient Characteristic	Primary Endpoint	PFS			OS			ORR (%)
					Median (months)	HR	HR, 95% CI	Median (months)	HR	HR, 95% CI	
GOG218	TC+PL	625	Newly diagnosed	PFS	10.3	0.770	0.681-0.870	39.3	0.885	0.750-1.040	NR
	TC+Bev+Bev(m)	623			14.1			39.7			NR
ICON7	TC	764	Newly diagnosed	PFS	17.5	0.930	0.830-1.050	58.6	0.990	0.850-1.140	48.0
	TC+Bev+Bev(m)	764			19.9			58.0			67.0

Qualität der Studien:



Studienergebnisse:

Overall Survival



PFS

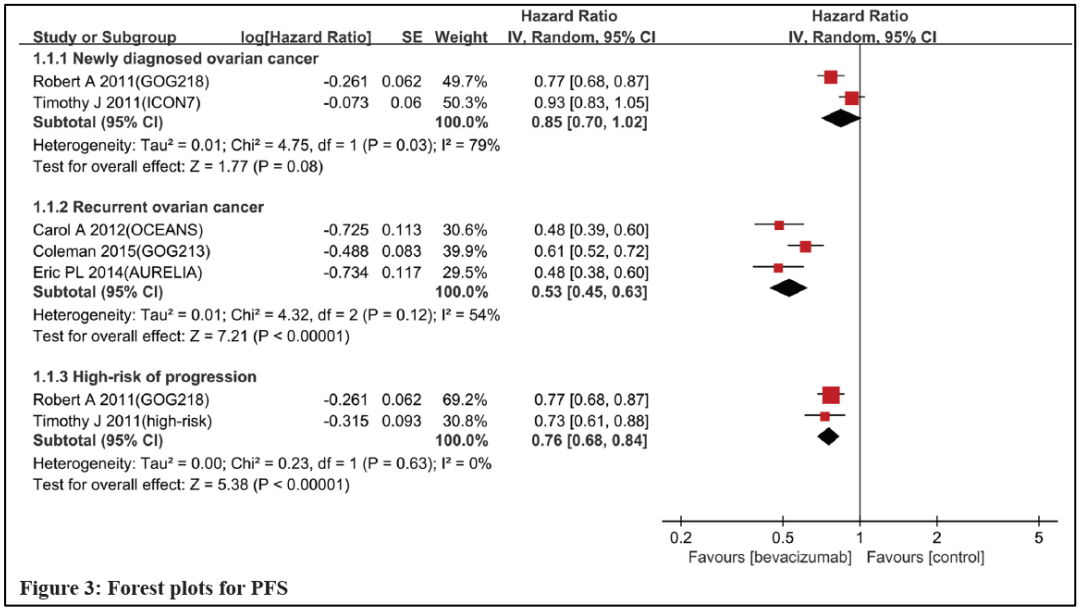


Figure 3: Forest plots for PFS

Anmerkung/Fazit der Autoren

In newly diagnosed ovarian cancer, the overall population had no statistical survival benefit according to the two trials, ICON7 and GOG-218. Remarkably, in patients with a high risk of progression, the evidence implies that bevacizumab confers a survival benefit. The addition of bevacizumab to first-line treatment in ovarian cancer would be a good option for patients with poor prognoses, such as stage III or IV patients after debulking surgery. However, the survival benefit of bevacizumab in high-risk patients was concluded from subgroup analysis.

3.4 Leitlinien

Leitlinienprogramm Onkologie, 2019 [2,3].

DGGG, DKG, Deutsche Krebshilfe, AWMF

S3-Leitlinie Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren, Version 3.0 – Januar 2019, AWMF-Registernummer: 032-035OL

Leitlinienorganisation/Fragestellung

Die Leitlinie „Diagnostik, Therapie und Nachsorge maligner Ovarialtumoren“ ist ein evidenz- und konsensusbasiertes Instrument zur Versorgung der Patientinnen mit Borderlinetumoren und bösartigen Tumoren der Eierstöcke, der Tuben und des Peritoneums einschließlich der Keimstrang-Stroma- und Keimzelltumoren.

Methodik

Grundlage der Leitlinie

- Interdisziplinäre LL-Entwicklungsgruppe
- Interessenskonflikte dargelegt und Umgang beschrieben
- Strukturierte Konsensfindung
- Gültigkeit der Leitlinie: ca. 3 Jahre

Recherche/Suchzeitraum:

- Recherche für Version 2.1. Aktualisierungsrecherchen von 1.3.2016 – 30.06.2017; auf RCT beschränkt; Version 2.: Recherche von Primärstudien bis 03.2016; Version 1: Leitlinienadaptionen und syst. Literaturrecherche bis 2010

Änderungen bzw. Neuerungen in der Version 2.1.

- Die Aktualisierung der Leitlinie zwischen 2017 und 2018 führten zu einigen relevanten Änderungen. Neue Studienergebnisse führten in den Bereichen Vorläuferformen des Ovarialkarzinoms, genetische Beratung, molekularpathologische Marker, Kombinations-Chemotherapieregime, HIPEC, Einsatz von PARP-Inhibitoren und Keimstrang-Stromatumoren zu geänderten oder neuen Empfehlungen.

LoE

Grad	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, systematische Übersichten von RCTs oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, systematische Übersichten von RCTs oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder Qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist

2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

GoR

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	soll
B	Empfehlung	sollte
0	Empfehlung offen	kann

Empfehlungen

7.3.4. OP-Zeitpunkt und präoperative Chemotherapie

7.11.	Evidenzbasiertes Statement	geprüft 2018
Level of Evidence 1+	Es gibt keinen Vorteil für eine primäre Chemotherapie gefolgt von einer Intervalloperation.	
	Leitlinien: SIGN [4] Primärstudien: [314-319]	

7.12.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Als Therapiefolge soll die Primäroperation gefolgt von einer Chemotherapie durchgeführt werden.	
Level of Evidence 1+	Leitlinien: SIGN [4] Primärstudien: [314-319]	

Die Frage des optimalen Operationszeitpunktes beim fortgeschrittenen Ovarialkarzinom wird seit vielen Jahren kontrovers diskutiert. Auf Basis von 3 großen und einer kleineren, randomisierten Phase-III-Studie lässt sich mittlerweile eine klare Empfehlung für die primäre Debulking-Operation und gegen eine neoadjuvante Chemotherapie gefolgt von Intervall-OP und postoperativer Chemotherapie aussprechen [314, 316-318].

314. Vergote, I., et al., Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med, 2010. 363(10): p. 943-53.
316. van der Burg, M.E., et al., The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. Gynecological Cancer Cooperative Group of the European Organization for Research and Treatment of Cancer. N Engl J Med, 1995. 332(10): p. 629-34.
317. Rose PG, et al., A phase III randomized study of interval secondary cytoreduction in patients with advanced stage ovarian carcinoma with suboptimal residual disease: a Gynecologic Oncology Group study. American Society of Clinical Oncology, 2002.
318. Redman, C.W., et al., Intervention debulking surgery in advanced epithelial ovarian cancer. Br J Obstet Gynaecol, 1994. 101(2): p. 142-6. Systemische Primärtherapie des fortgeschrittenes Ovarialkarzinoms

8.5.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Die First-line-Chemotherapie für Patientinnen mit fortgeschrittenem Ovarialkarzinom (IIB–IV) soll aus Carboplatin AUC 5 und Paclitaxel 175 mg/m² über 3 h i.v. für insgesamt 6 Zyklen alle 3 Wochen bestehen.	
Level of Evidence 1++	Leitlinien: NICE 2011 [365], NHS TA91 [366], SIGN 135 [367] Primärstudien: [368-379]	

8.6.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad 0	Beim fortgeschrittenen Ovarialkarzinom (IIIB–IV) kann eine zusätzliche Behandlung mit Bevacizumab erwogen werden.	
Level of Evidence 1+	Primärstudien: [380-382]	

Die derzeitige Standard-Chemotherapie beim fortgeschrittenen Ovarialkarzinom besteht aus 6 Zyklen Carboplatin (AUC 5)/ Paclitaxel (175 mg/m2 über 3 h i.v.) im Anschluss an die Operation.

Die Kombination aus beiden Substanzen ist nach dem Ergebnis einer Metaanalyse der hierzu vorhandenen Studien der taxanfreien Platintherapie hinsichtlich progressionsfreiem Überleben und Gesamtüberleben überlegen [367]. In einer prospektiv randomisierten Multicenterstudie konnte bei unterschiedlichem Toxizitätsprofil ein Vorteil von Docetaxel gegenüber Paclitaxel beim fortgeschrittenen Ovarialkarzinom nicht nachgewiesen werden (negative Studie, da sie darauf ausgelegt war, einen Vorteil von Carboplatin/Docetaxel gegenüber Carboplatin/Paclitaxel zu zeigen) [374]. Die Rate an Hämatotoxizität war unter Docetaxel, das Auftreten sensorischer Neurotoxizität unter Paclitaxel erhöht. Carboplatin ist Substanz der Wahl beim Ovarialkarzinom aufgrund der Äquieffektivität zu Cisplatin und der im Vergleich zu Cisplatin besseren Verträglichkeit in Hinblick auf Nausea, Emesis und Neurotoxizität und überlegene Lebensqualität [369].

Bevacizumab

Die Gabe von Bevacizumab parallel zur Chemotherapie und als Erhaltungstherapie für insgesamt 12 bzw. 15 Monate konnte in 2 Phase-III-Studien das progressionsfreie Überleben signifikant verlängern [371, 372]. Das Gesamtüberleben war lediglich in Subgruppen signifikant verbessert (hohe Tumorlast, Stadium IV oder high-grad-seröser Subtyp), eine Verschlechterung der Lebensqualität war gering aber signifikant [373, 375, 376].

Intraperitoneale Chemotherapie

Zur intraperitonealen Chemotherapie zeigen 4 von 7 randomisierten Phase-III-Studien keinen signifikanten Vorteil. In 2 der 3 größeren Phase-III-Studien der GOG, Protokoll 104 und 172, wurde ein statistisch signifikanter Überlebensvorteil durch die intraperitoneale Chemotherapie nachgewiesen, in der GOG 114 ein signifikanter Vorteil im progressionsfreien Überleben, aber nicht im Gesamtüberleben [380]. In der zuletzt publizierten GOG-172-Studie wurde Cisplatin/Paclitaxel i.v. mit Paclitaxel i.v. gefolgt von Cisplatin i.p. am Tag 2 und Paclitaxel i.p. am Tag 8 verglichen. Das Hauptproblem der i.p. Therapie war in der GOG-172-Studie die ausgeprägte Toxizität. Nur 42 % der Patientinnen erhielten die i.p. Therapie wie geplant, 8 % erhielten keine i.p. Therapie und 34 % nur 1–2 Zyklen. Eine aktuell vorgestellte Studie (GOG 252), die intraperitoneale Therapien mit einer intravenösen Therapie verglich zeigte keinen Vorteil durch Wahl eines intraperitonealen Applikationsweges. Zur hyperthermen intraperitonealen Chemotherapie (HIPEC) gibt es derzeit nur Daten aus Phase-II-Studien, in denen heterogene Therapieregime in kleinen Patientinnenkollektiven untersucht wurden. Daher sollten gegenwärtig i.p. Chemotherapie sowie HIPEC/PIPAC nicht außerhalb kontrollierter klinischer Studien eingesetzt werden.

356. NICE. NICE Clinical Guideline 122. The Recognition and Initial Management of Ovarian Cancer. 2011 [cited 2012 September 7]; Available from: http://guidance.nice.org.uk/CG122.
357. NHS National Institute for Health and Clinical Excellence. Technology Appraisal Guidance 91 Paclitaxel, pegylated liposomal doxorubicin hydrochloride and topotecan for second-line or subsequent treatment of advanced ovarian cancer. 2005 [cited 2012 September 7]; Available from: http://www.nice.org.uk/TA091.
358. Scottish Intercollegiate Guidelines Network, SIGN #135: Management of epithelial ovarian cancer. Vol. 135. 2013, Edinburgh: Scottish Intercollegiate Guidelines Network,.
359. ICON2: randomised trial of single-agent carboplatin against three-drug combination of CAP (cyclophosphamide, doxorubicin, and cisplatin) in women with ovarian cancer. ICON Collaborators. International Collaborative Ovarian Neoplasm Study. Lancet, 1998. 352(9140): p. 1571-6.
360. Paclitaxel plus carboplatin versus standard chemotherapy with either single-agent carboplatin or cyclophosphamide, doxorubicin, and cisplatin in women with ovarian cancer: the ICON3 randomised trial. Lancet, 2002. 360(9332): p. 505-15.

361. McGuire, W.P., et al., Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. N Engl J Med, 1996. 334(1): p. 1-6.
362. Muggia, F.M., et al., Phase III randomized study of cisplatin versus paclitaxel versus cisplatin and paclitaxel in patients with suboptimal stage III or IV ovarian cancer: a gynecologic oncology group study. J Clin Oncol, 2000. 18(1): p. 106-15.
363. Neijt, J.P., et al., Exploratory phase III study of paclitaxel and cisplatin versus paclitaxel and carboplatin in advanced ovarian cancer. J Clin Oncol, 2000. 18(17): p. 3084-92.
364. Piccart, M.J., et al., Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. J Natl Cancer Inst, 2000. 92(9): p. 699-708.
365. West, R.J. and S.F. Zweig, Meta-analysis of chemotherapy regimens for ovarian carcinoma: a reassessment of cisplatin, cyclophosphamide and doxorubicin versus cisplatin and cyclophosphamide. Eur J Gynaecol Oncol, 1997. 18(5): p. 343-8.
366. Ozols, R.F., Chemotherapy for ovarian cancer. Semin Oncol, 1999. 26(6 Suppl 18): p. 34-40.
367. du Bois, A., J.P. Neijt, and J.T. Thigpen, First line chemotherapy with carboplatin plus paclitaxel in advanced ovarian cancer--a new standard of care? Ann Oncol, 1999. 10 Suppl 1: p. 35-41.
368. Aabo, K., et al., Chemotherapy in advanced ovarian cancer: four systematic meta-analyses of individual patient data from 37 randomized trials. Advanced Ovarian Cancer Trialists' Group. Br J Cancer, 1998. 78(11): p. 1479-87.
369. du Bois, A., et al., A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. Journal of the National Cancer Institute, 2003. 95(17): p. 1320-1329.
370. Ozols, R.F., et al., Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol, 2003. 21(17): p. 3194-200.
371. Burger, R.A., et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med, 2011. 365(26): p. 2473-83.
372. Perren, T.J., et al., A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med, 2011. 365(26): p. 2484-96.
373. Oza, A.M., et al., Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol, 2015. 16(8): p. 928-36.

8.3.Einsatz von HIPEC

8.7.	Evidenzbasiertes Statement	neu 2018
Level of Evidence 1+	Bisher liegen keine überzeugenden Daten vor, die den Einsatz von HIPEC bei Patientinnen mit Ovarialkarzinom rechtfertigen.	
	Primärstudien: [1]	

Die Ergebnisse der ersten Phase-III-Studie zur hyperthermen intraperitonealen Chemotherapie (HIPEC) wurden 2018 vollpubliziert [1]. Hier wurde HIPEC in einer speziellen therapeutischen Situation, nämlich nach vorangegangener neoadjuvanter Chemotherapie (NAC) wegen initial als nicht operabel eingestufter Tumorerkrankung untersucht. 245 Patientinnen mit einem Ovarialkarzinom FIGO III nach NAC mit mindestens stabiler Erkrankung nach 3 Zyklen Carboplatin/Paclitaxel wurden randomisiert. Im Rahmen der Intervalloperation wurde dann entweder eine HIPEC mit Cisplatin 100mg/m2 oder keine HIPEC gegeben. Anschliessend wurden postoperativ weitere 3 Zyklen Carboplatin/Paclitaxel intravenös gegeben. Primäres Studienziel war das rückfallfreie Überleben (RFS). Hierfür fand sich in der ITT-Analyse für die HIPEC Gruppe eine signifikante Verbesserung (HR 0.66, 95 % CI 0.50-0.87, p= 0.003). Das mediane RFS war 10.7 Monate im Standardarm vs. 14.2 Monate im HIPEC-Arm. Das mediane Gesamtüberleben war 33.9 Monate im Standardarm vs. 45.7 Monate im HIPEC-Arm. Grad 3/4 unerwünschte Ereignisse waren mit 27 % (HIPEC) vs 25 % (Standard) nicht unterschiedlich.

Die Studie wirft erhebliche Fragen auf und sorgt für Diskussionen [1, 390, 391]. Es gibt Probleme bei der Selektion der Patientinnen, so sind zunächst einmal keine Kriterien für als „inoperabel“ eingestufte Patientinnen definiert worden. Diese erfolgte entweder nach Einschätzung des Behandlers (90 %) oder erfolgloser OP (10 %). Dann wurde an nicht näher definierten Behandlungszentren die NAC begonnen, im Anschluss in einem der 8 Studienzentren beurteilt ob die Intervall-OP „erfolgversprechend“ im Sinne von „optimal Debulking <1cm“ sein würde, dann erfolgte die „Registrierung“ in die Studie und intra-operativ die Randomisation. Auch bei der Auswahl der Zentren und Operateure gibt es Unklarheiten. So erfolgte die Auswahl der Zentren nach dem Vorhandensein einer HIPEC-Maschine, über die (chirurgische) Qualifikation der Operateure ist nichts berichtet. Die 245 Pat wurden in 9 Jahren rekrutiert, d.h. also 27 pro Jahr. Verteilt auf die 8 Zentren bedeutet dies 3 Pat./Zentrum/Jahr. Da das Netherlands Cancer Institute fast die Hälfte der Pat. (105) eingeschlossen hat, ist die Verzerrung vermutlich noch höher. Es findet sich „nur“ in 70 % eine Komplettresektion bei Intervalldebulking. Die Darmresektionsrate ist angemessen, aber die Rate an Stomaanlagen mit 72 % im HIPEC Arm sehr hoch. Auch die Datenqualität insgesamt wirft Fragen auf: Nur 20 % Alopezierate bei 6 Zyklen Carboplatin/Paclitaxel ist zumindest ungewöhnlich. Es werden keine Lebensqualitätsdaten berichtet, auch die chirurgischen Komplikationsraten sind nicht berichtet. Auch von statistischer Seite gibt es kritische Aspekte: Eigentlich sollte die Randomisation intraoperativ erfolgen, was zur Vermeidung von Verzerrungen sinnvoll ist. In 2 von 8 Zentren wurde diese aber aus logistischen Gründen, um keinen teuren HIPEC Techniker vergeblich vorzuhalten, präoperativ vorgenommen. Damit kann eine Beeinflussung der Intention des Operateurs nicht ausgeschlossen werden. Auch die Fallzahl ist relativ klein, die Differenz im Überleben zwischen den beiden Behandlungsarmen beruht auf 15 Ereignissen. Es gibt keine Stratifikation für wichtige prognostische Faktoren, sei es das Substadium, den BRCA-Mutationsstatus oder den histologischen Typ, was weitere Verzerrungen mit sich bringen kann.

Aufgrund dieser Fragen und möglicher Verzerrungen können die Ergebnisse nicht dazu beitragen, HIPEC als neuen Standard zu definieren. Hier müssen die Ergebnisse weiterer Studien, die bereits durchgeführt worden sind, abgewartet werden.

1. van Driel, W.J., et al., Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med, 2018. 378(3): p. 230-240.
390. Vergote, I., L. Chiva, and A. du Bois, Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N Engl J Med, 2018. 378(14): p. 1362-3.
391. Fotopoulou, C., et al., HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer? Ann Oncol, 2018. 29(8): p. 1610-1613.

Erhaltungs-/Konsolidierungstherapien

8.9.	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad **A**	Erhaltungs-/Konsolidierungstherapien nach Abschluss der Primärtherapie sollen nicht durchgeführt werden*. *Für die Wirksamkeit einer Konsolidierungs- oder Erhaltungstherapie im Hinblick auf PFS liegen nur Daten für Antiangiogenetische Therapien vor (siehe 8.6.)	
Level of Evidence **1+**	Primärstudien: [380, 381, 408-415]	

Eine Erhaltungs- bzw. Konsolidierungstherapie beschreibt die Therapie über die klinische, radiologische oder serologische Komplettremission hinaus bzw. über die Applikation von 6 Zyklen Carboplatin/Paclitaxel hinaus. Diese wurde sowohl für zytostatische Therapie (z. B. Paclitaxel-Erhaltungstherapie) als auch z. B. Strahlentherapie in Studien untersucht, ohne dass ein reproduzierbarer Vorteil hinsichtlich des progressionsfreien Überlebens oder Gesamtüberlebens der Patientinnen beobachtet werden konnte [371, 372, 397-404].

Einzig für die Wirksamkeit einer Erhaltungs- bzw. Konsolidierungstherapie mit Bevacizumab liegen Daten in Hinblick auf eine Verlängerung des progressionsfreien Überlebens vor (siehe Empfehlung 8.6.).

Subgruppen

Die überwiegende Mehrzahl der fortgeschrittenen Ovarialkarzinome sind seröse „high-grade“ Karzinome (zumeist G3). In molekularen Untersuchungen unterscheiden sich diese deutlich von serösen „low-grade“ Karzinomen sowie anderen histologischen Subtypen wie muzinösen, endometrioiden oder klarzelligen Karzinomen. Es gibt Anzeichen dafür, dass das Ansprechen der verschiedenen molekularen und histologischen Subtypen sich hinsichtlich bestimmter Therapien ebenfalls unterscheidet. Muzinöse Ovarialkarzinome beispielsweise sprechen vermeintlich schlechter auf Carboplatin/Paclitaxel an, ebenso scheint das Ansprechen von G1-Tumoren deutlich geringer zu sein als bei G3-Tumoren. Da die bisherigen Erkenntnisse hierzu jedoch nur hypothesengenerierend sind, kann derzeit eine Abweichung vom Therapiestandard für einzelne Subgruppen von Patientinnen nicht empfohlen werden [257, 291, 305, 313, 416-433].

257. Kommoss, S., et al., Independent prognostic significance of cell cycle regulator proteins p16(INK4a) and pRb in advanced-stage ovarian carcinoma including optimally debulked patients: a translational research subprotocol of a randomised study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group. Br J Cancer, 2007. 96(2): p. 306-13.
291. du Bois, A., et al., Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer, 2009. 115(6): p. 1234-44.
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371. Burger, R.A., et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med, 2011. 365(26): p. 2473-83.
372. Perren, T.J., et al., A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med, 2011. 365(26): p. 2484-96
397. Lambert, H.E., et al., A randomized trial of five versus eight courses of cisplatin or carboplatin in advanced epithelial ovarian carcinoma. A North Thames Ovary Group Study. Ann Oncol, 1997. 8(4): p. 327-33.
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Colombo N et al., 2019 [1].

ESMO, ESGO

ESMO–ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†

Leitlinienorganisation/Fragestellung

The objectives of these recommendations are to improve and to harmonise the management of patients with ovarian cancer.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;

Recherche/Suchzeitraum:

- January 2007 and December 2017 was carried out using the Medline database

LoE/GoR

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [2].

Sonstige methodische Hinweise

- Keine Angaben zu Aktualisierungen der Leitlinie
- Keine Angaben, ob eine externe Begutachtung der Leitlinie vorgesehen war.
- „Funding: All costs relating to the consensus conference were covered from ESMO and ESGO funds. There was no external funding of the event or manuscript production."

Empfehlungen

11. How to select patients for primary debulking surgery or neoadjuvant chemotherapy?

Recommendation 11.1: the selection of patients for primary debulking surgery or neoadjuvant treatment must be carried out in a specialist ovarian cancer centre, according to the ESGO Quality recommendations 2016 [191] in a multidisciplinary Setting

- Level of evidence: IV Strength of recommendation: A
- Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 11.2: complete tumour resection at upfront debulking is the most important prognostic factor for patients with advanced ovarian cancer and is the main goal of surgery.

- Level of evidence: IV Strength of recommendation: A
- Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Recommendation 11.3: when complete surgery with no macroscopic visible disease appears feasible (both spread of disease and general condition of the patient), primary upfront debulking should be offered.

- Level of evidence: IV Strength of recommendation: B
- Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

Complete resection of all macroscopic disease has been shown to be the single most important independent prognostic factor in advanced EOC [172, 173] and careful evaluation of patients before surgery is essential to defining the management plan [174]. If resection of all macroscopic disease can be obtained based on pre-operative staging with an acceptable operative morbidity, upfront debulking surgery (UDS) followed by carboplatin/paclitaxel is standard of care [175, 176]. The EORTC55971 trial [177] and the CHORUS trial [178] showed a similar PFS and OS for patients with stage IIIC or IV disease receiving NACT and interval debulking surgery (IDS) compared with UDS. As both studies contained low percentages of patients with complete UDS (<20%), the Trial on Radical Upfront Surgical Therapy (TRUST), including a qualification process for participating centres, is currently ongoing.

172. du Bois A, Reuss A, Pujade-Lauraine E et al. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer 2009; 115(6): 1234–1244.
173. Bristow RE, Tomacruz RS, Armstrong DK et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002; 20(5): 1248–1259.
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12. What is the current role of bevacizumab in first-line treatment?

Recommendation 12.1: bevacizumab (15 mg/kg or 7.5 mg/kg every 3 weeks for maximum of 15 months) improves PFS in patients with stage III–IV ovarian cancer and should be considered in addition to carboplatin and paclitaxel.

- Level of evidence: I Strength of recommendation: A
- Consensus: 97.5% (39) yes, 0% (0) no, 2.5% (1) abstain (40 voters)

Recommendation 12.2: bevacizumab in the neoadjuvant setting can be considered, although additional improvement in efficacy is not proven with level I evidence.

- Level of evidence: II Strength of recommendation: B
- Consensus: 97.5% (39) yes, 2.5% (1) no, 0% (0) abstain (40 voters)

Recommendation 12.3: bevacizumab can be safely administered in the neoadjuvant setting before and after IDS providing the interval between surgery and administration is at least 4–6 weeks.

- Level of evidence: II Strength of recommendation: B
- Consensus: 100% (40) yes, 0% (0) no, 0% (0) abstain (40 voters)

GOG 218 [192], a placebo-controlled phase III trial, randomised patients with incompletely resected stage III or any stage IV newly diagnosed EOC to either carboplatin/paclitaxel with or without bevacizumab (15 mg/kg) followed by placebo or bevacizumab maintenance treatment up to 21 cycles; significant increase in PFS was shown in patients receiving bevacizumab for 21 cycles. The ICON7 trial [193] included patients with high-risk, early-stage disease (stage I or IIA and clear cell or grade 3 tumours) or advanced-stage IIB to IV tumours. Despite lower dosage and fewer cycles of bevacizumab (7.5 mg/kg for 18 cycles) used in the ICON7 trial, PFS results were similar [193].

Neither the GOG 218 trial nor the ICON7 trial showed an OS benefit in the overall study populations [192, 193] but post hoc subgroup analysis indicated statistically significant OS benefit in patients with stage IV disease in GOG 218 [194] and patients at high risk of progression (i.e. FIGO stage III with >1 cm residual disease or stage IV) in the ICON7 trial [22].

Bevacizumab-related toxicities are usually mild. The most common toxicities are grade 2 hypertension and grade 3 proteinuria. The incidence is positively correlated with higher dose and longer duration [192, 193]. Furthermore, the ICON7 and GOG 218 trials showed a trend towards more mucocutaneous bleeding, grade 3 thromboembolic events and gastrointestinal adverse events (AEs) [192, 193, 195]. Regarding gastrointestinal toxicity, the most common AE was perforation (1.1%), followed by haemorrhage (0.8%) and fistula formation (0.7%) [22, 195].

Regarding the administration of bevacizumab with NACT, two smaller RCTs, the ANTHALYA and GEICO 1205/NOVA openlabel phase II trials [196, 197], were carried out. Patients received 4 cycles of neoadjuvant carboplatin/paclitaxel with or without at least 3 cycles of bevacizumab (15mg/kg) followed by IDS [196,197]. Bevacizumab was stopped 4–5 weeks before surgery and restarted at least 7 weeks after IDS in the ANTHALYA trial [196], compared with 6 weeks before and 6 weeks after surgery in the GEICO 1205/NOVA trial [197]. In the ANTHALYA trial [196], complete resection rate (CRR) was significantly higher with additional bevacizumab compared with CRR previously reported in the EORTC study [177]. In contrast, the GEICO 1205/NOVA trial [197] showed no benefit in the complete macroscopic response rate (PCI¼0) but found an enhanced rate of surgical operability. Both studies showed similar safety profiles, with no increase in toxicity (grade 3 haematological, gastrointestinal and vascular AEs) compared with carboplatin/paclitaxel therapy when adequate patient selection was carried out. Therefore, bevacizumab in the neoadjuvant setting is considered safe and may improve surgical outcome.

192. Burger RA, Brady MF, Bookman MA et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. N Engl J Med 2011; 365(26): 2473–2483.
193. Perren TJ, Swart AM, Pfisterer J et al. A phase 3 trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365(26): 2484–2496.
194. Randall LM, Burger RA, Nguyen H et al. Outcome differences in patients with advanced epithelial ovarian, primary peritoneal and fallopian tube cancers with and without bevacizumab. Gynecol Oncol 2013; 130: e33–e34.
195. Burger RA, Brady MF, Bookman MA et al. Risk factors for GI adverse events in a phase III randomized trial of bevacizumab in first-line therapy of advanced ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2014; 32(12): 1210–1217.
196. Rouzier R, Gouy S, Selle F et al. Efficacy and safety of bevacizumabcontaining neoadjuvant therapy followed by interval debulking surgery in advanced ovarian cancer: results from the ANTHALYA trial. Eur J Cancer 2017; 70: 133–142.

14. Is there a place for intraperitoneal chemotherapy and hyperthermic intraperitoneal chemotherapy?

Recommendation 14.1: i.p. chemotherapy is not a standard of care as first-line treatment.

- Level of evidence: I Strength of recommendation: A
- Consensus: 95% (38) yes, 0% (0) no, 5% (2) abstain (40 voters)

Recommendation 14.2: HIPEC is not a standard of care as first-line treatment.

- Level of evidence: II Strength of recommendation: A

- Consensus: 95% (38) yes, 0% (0) no, 5% (2) abstain (40 voters)

Several studies have been published, but due to their small sample size, incomparable treatment protocols and high levels of toxicity, intraperitoneal (i.p.) chemotherapy was not recommended for routine use [203–206].

The GOG 172 trial randomized patients with stage III disease to either 3-weekly intravenous (i.v.) cisplatin/paclitaxel or i.v. paclitaxel followed by i.p. cisplatin/ paclitaxel and showed a remarkable improvement in OS [207] persisting even after 10 years [208]. Despite these promising results, toxicity with i.p. (e.g. grade 3–4 leukopaenia, gastrointestinal/ renal AEs, infection and pain) was significantly higher with lower QoL and a lower completion rate [207] for 6 i.p. cycles compared with previous reported studies [203, 204]. Moreover, the absence of an ITT analysis, the higher dosage of paclitaxel/cisplatin in the i.p. arm, the imbalance in PFS/OS benefit ratio and the low OS in the control group compared with published data [209, 210] further limit the clinical relevance and implementation of i.p. therapy in ovarian cancer [211].

To address the pitfalls of the GOG 172 trial, a phase III RCT (GOG 252) [212] was carried out on patients with stage II–IV EOC. As the first trial comparing i.p. and i.v. administration of similar doses of chemotherapy, the GOG 252 trial [212] did not confirm PFS improvement with i.p. chemotherapy (presented at SGO 2016, still unpublished). Moreover, i.v. chemotherapy was better tolerated than i.p. chemotherapy.

203. Markman M, Bundy BN, Alberts DS et al. Phase III trial of standarddose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J Clin Oncol 2001; 19(4): 1001–1007.
204. Alberts DS, Liu PY, Hannigan EV et al. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N Engl J Med 1996; 335(26): 1950–1955.
205. Hess LM, Benham-Hutchins M, Herzog TJ et al. A meta-analysis of the efficacy of intraperitoneal cisplatin for the front-line treatment of ovarian cancer. Int J Gynecol Cancer 2007; 17(3): 561–570.
206. Jaaback K, Johnson N, Lawrie TA. Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. Cochrane Database Syst Rev 2016; (1): CD005340.
207. Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006; 354(1): 34–43.
208. Tewari D, Java JJ, Salani R et al. Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2015; 33(13): 1460–1466.
209. Ozols RF, Bundy BN, Greer BE et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. J Clin Oncol 2003; 21(17): 3194–3200.
210. du Bois A, Lu¨ck HJ, Meier W et al. A randomized clinical trial of cisplatin paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. J Natl Cancer Inst 2003; 95(17): 1320–1329.
211. Gore M, du Bois A, Vergote I. Intraperitoneal chemotherapy in ovarian cancer remains experimental. J Clin Oncol 2006; 24(28): 4528–4530.
212. Walker J, Brady MF, DiSilvestro PA et al. A phase III trial of bevacizumab with IV versus IP chemotherapy for ovarian, fallopian tube, and peritoneal carcinoma: an NRG oncology study. Gynecol Oncol 2016; 141(1): 208.

<u>Advanced (FIGO III and IV) non-high-grade serous ovarian cancer in first line.</u>

Recommendation 15.1: primary debulking surgery with no macroscopic residual disease is of pivotal importance due the low chemosensitivity in low-grade serous, mucinous and clear cell ovarian carcinoma.

- Level of evidence: IV Strength of recommendation: A
- Consensus: 100%(38) yes, 0% (0) no, 0% (0) abstain (38 voters)

Recommendation 15.2: even debulking with residual disease <1 cm in low-grade serous ovarian cancer may improve survival when complete cytoreduction is not feasible.

- Level of evidence: IV Strength of recommendation: C
- Consensus: 100%(38) yes, 0% (0) no, 0% (0) abstain (38 voters)

Recommendation 15.3: carboplatin in combination with paclitaxel is the standard chemotherapy. Addition of bevacizumab should be considered.

- Level of evidence: I Strength of recommendation: B
- Consensus: 97.4% (37) yes, 0% (0) no, 2.6% (1) abstain (38 voters)

Recommendation 15.4: maintenance antioestrogen therapy after chemotherapy can be considered in low-grade serous ovarian cancer.

- Level of evidence: IV Strength of recommendation: C
- Consensus: 92.1% (35) yes, 0% (0) no, 7.9% (3) abstain (38 voters)

> Similar to HGSC, optimal surgical treatment is the keystone of the treatment of advanced low-grade serous ovarian cancer [172, 226]. Regarding the less chemosensitive nature of low-grade serous ovarian cancer, even debulking with residual disease <1 cm may improve survival when complete cytoreduction is not feasible and can be an option. […]
>
> While carboplatin/ paclitaxel is still the standard systemic therapy in lowgrade serous ovarian cancer, multiple retrospective studies showed lower response rates and less survival benefit from chemotherapy compared with high-grade serous ovarian cancer, implicating a limited chemosensitivity [228–231]. Similar findings were found in mucinous [45, 232] and clear cell EOCs [233, 234]. Being less chemosensitive, the role of surgery is enhanced and novel therapeutic strategies for systemic treatment of lowgrade serous ovarian cancer are being investigated (e.g. antihormonal and targeted therapies)
>
> Bevacizumab has shown activity in low-grade serous ovarian cancer in first-line and recurrent settings in three small retrospective cohorts [238–240].

226. Fader AN, Java J, Ueda S et al. Survival in women with grade 1 serous ovarian carcinoma. Obstet Gynecol 2013; 122(2): 225–232.
228. Schmeler KM, Sun CC, Malpica A et al. Low-grade serous primary peritoneal carcinoma. Gynecol Oncol 2011; 121(3): 482–486.
229. Schmeler KM, Sun CC, Bodurka DC et al. Neoadjuvant chemotherapy for low-grade serous carcinoma of the ovary or peritoneum. Gynecol Oncol 2008; 108(3): 510–514.
230. Grabowski JP, Harter P, Heitz F et al. Operability and chemotherapy responsiveness
in advanced low-grade serous ovarian cancer. An analysis of the AGO Study Group metadatabase. Gynecol Oncol 2016; 140(3): 457–462.
231. Gockley A, Melamed A, Bregar AJ et al. Outcomes of women with highgrade and low-grade advanced-stage serous epithelial ovarian cancer. Obstet Gynecol 2017; 129(3): 439–447.
232. Hess V, A'Hern R, Nasiri N et al. Mucinous epithelial ovarian cancer: a separate entity requiring specific treatment. J Clin Oncol 2004; 22(6): 1040–1044.
233. Magazzino F, Katsaros D, Ottaiano A et al. Surgical and medical treatment of clear cell ovarian cancer: results from the Multicenter Italian Trials in Ovarian Cancer (MITO) 9 retrospective study. Int J Gynecol Cancer 2011; 21(6): 1063–1070.
234. Goff BA, Sainz de la Cuesta R, Muntz HG et al. Clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy in stage III disease. Gynecol Oncol 1996; 60(3): 412–417.
235. Fader AN, Bergstrom J, Jernigan A et al. Primary cytoreductive surgery and adjuvant hormonal monotherapy in women with advanced lowgrade serous ovarian carcinoma: reducing overtreatment without compromising survival? Gynecol Oncol 2017; 147(1): 85–91.
236. Gershenson DM, Bodurka DC, Coleman RL et al. Hormonal maintenance therapy for women with low-grade serous cancer of the ovary or peritoneum. J Clin Oncol 2017; 35(10): 1103–1111.
237. Farley J, Brady WE, Vathipadiekal V et al. Selumetinib in women with recurrent low-grade serous carcinoma of the ovary or peritoneum: an open-label, single-arm, phase 2 study. Lancet Oncol 2013; 14(2): 134–140.
238. Grisham RN, Iyer G, Sala E et al. Bevacizumab shows activity in patients with low-grade serous ovarian and primary peritoneal cancer. Int J Gynecol Cancer 2014; 24(6): 1010–1014.
239. Rose PG, Mahdi H, Jernigan A, Yang B. Activity of bevacizumab in patients with low-grade serous ovarian carcinoma. Int J Gynecol Cancer 2016; 26(6): 1048–1052.
240. Dalton HJ, Fleming ND, Sun CC et al. Activity of bevacizumabcontaining regimens in recurrent low-grade serous ovarian or peritoneal cancer: a single institution experience. Gynecol Oncol 2017; 145(1): 37–40.

Scottish Intercollegiate Guidelines Network (SIGN), 2013/2018 [10].

Management of epithelial ovarian cancer - Revised 2018

Leitlinienorganisation/Fragestellung

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- 2003-2012

LoE

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case control or cohort studies
High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies, eg case reports, case series
4 Expert opinion

GoR

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.
A At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; *or*
A body of evidence consisting principally of studies rated as 1+,
directly applicable to the target population, and demonstrating overall consistency of results
B A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 1++ or 1+
C A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or*
Extrapolated evidence from studies rated as 2++
D Evidence level 3 or 4; *or*
Extrapolated evidence from studies rated as 2+
GOOD PRACTICE POINTS: Recommended best practice based on the clinical experience of the guideline development group

Sonstige methodische Hinweise

- Update der Empfehlungen zu PARP-Inhibitoren, Bevazizumab, Niraparib

- Kein Recherchedatum für Update genannt

Empfehlungen

5.4.1. CYTOREDUCTIVE SURGERY

In surgery for advanced ovarian cancer, the aim should be to achieve complete cytoreduction. **LoE 2++ GoE C**

5.4.2. NEOADJUVANT CHEMOTHERAPY AND DELAYED PRIMARY SURGERY

The use of neoadjuvant chemotherapy in women with stage IIIc or IV ovarian cancer may be considered as an alternative to primary debulking surgery. **LoE 1++ GoE A**

- With regard to selecting who will benefit from neoadjuvant chemotherapy, treatment should be individualised to the patient taking into account resectability, age, histology, performance status and after ruling out the possibility of other primary tumours, and after full discussion at multidisciplinary team meetings.

As the majority (65%) of patients with ovarian cancer present with advanced disease and most of these will have stage III or IV disease, the adoption of NACT has the potential to reduce postoperative morbidity without any adverse effect on overall survival. NACT could also reduce delays in starting treatment as the main factor causing delay is getting a date for surgery within two weeks after the diagnosis has been made.

6.2.1 ROLE OF PLATINUM AGENTS

A First line chemotherapy treatment of epithelial ovarian cancer should include a platinum agent either in combination or as a single agent, unless specifically contraindicated. **LoE 1++ GoE A**

Meta-analyses show significant benefit for use of platinum.128,129

6.2.2 CHOICE OF PLATINUM AGENTS

A Carboplatin is the platinum drug of choice in both single and combination therapy. **LoE 1++ GoE A**

The platinum based drugs cisplatin and carboplatin are equally efficacious in the treatment of epithelial ovarian cancer.128 Carboplatin has a more favourable toxicity profile. The combination of carboplatin and paclitaxel is as efficacious as cisplatin and paclitaxel combination therapy.130

6.2.3 OTHER AGENTS

Paclitaxel is recommended in combination therapy with platinum in the first line post-surgery treatment of epithelial ovarian cancer where the potential benefits justify the toxicity of the therapy. In those unable to tolerate paclitaxel, peglated liposomal doxorubicin or gemcitabine in combination with carboplatin can be used as an alternative. **LoE 1++ GoE A**

A Patients who are unfit for combination therapy should be offered single agent carboplatin. **LoE 1++ GoE A**

A third cytotoxic agent should not be added to carboplatin and paclitaxel. **LoE 1++ GoE A**

6.2.5 BIOLOGICAL THERAPIES

Women with stage IV ovarian cancer should be offered bevacizumab in combination with carboplatin and paclitaxel. **LoE 1++ GoE A**

1++ Two RCTs (ICON7 GOG218) have investigated the benefit of the addition of bevacizumab, a humanised monoclonal antibody, to vascular endothelial growth factor A (VEGF), to carboplatin and paclitaxel.146,147

The GOG 218 study was a double-blind, placebo-controlled study of 1,873 patients with untreated stage III and IV disease (including 66% with stage IIIc and >1 cm residual disease or stage IV) and randomised between carboplatin (AUC 6) and paclitaxel (175 mg/m2) for six cycles plus bevacizumab 15 mg/kg during cycles 2–6 and placebo during cycles 7–22 or carboplatin and paclitaxel for six cycles plus bevacizumab during cycles 2–22.146 A limitation of this study was the change of the primary end point from OS to PFS as maintenance of the blinding after progression was not considered acceptable. Therefore, postprogression therapy was not controlled, so many patients crossed over to receive bevacizumab, affecting the integrity of OS data. There was no difference in PFS between the control group and bevacizumab initiation group but there was a statistically significant improvement in PFS for the group who received bevacizumab throughout (median 10.3 v 14.1 months, HR=0.717, 95% CI 0.625 to 0.824, p<0.001).

The ICON 7 study included 1,528 women with high-risk stage I-IIa and advanced stage IIb or IV epithelial ovarian cancer (9% had high risk early-stage disease, 70% had stage IIIc or IV ovarian cancer and 30% had stage IIIc >1 cm residual disease or stage IV). Patients were randomised between carboplatin (AUC, 5 or 6) and paclitaxel (175 mg/m2), given every three weeks for six cycles, or to this regimen plus bevacizumab (7.5mg/kg), given concurrently every three weeks for five or six cycles and continued for 12 additional cycles or until progression of disease. There was a small but statistically significant improvement in PFS in the whole population (restricted mean at 42 months was 22.4 months without bevacizumab v 24.1 months with bevacizumab p=0.04). In the women with stage IIIc and >1 cm residual disease or stage IV, the benefit was greater (PFS, restricted mean, at 42 months of 14.5 months v 18.1 months with respective median overall survival of 28.8 and 36.6 months; HR for death in the bevacizumab group of 0.64, 95% CI 0.48 to 0.85, p=0.002). Bevacizumab was associated with significantly higher rates of bleeding (mainly grade 1 mucocutaneous bleeding), hypertension of grade 2 or higher (18% with bevacizumab v 2% with standard therapy), thromboembolic events of grade 3 or higher (7% with bevacizumab v 3% with standard therapy), and gastrointestinal perforations (occurring in 10 patients in the bevacizumab group v three patients in the standard-therapy group). Quality of life scores did not differ between groups in either study.147

The addition of bevacizumab during and after chemotherapy, at both 7.5 mg/kg and 15 mg/kg, prolongs PFS and the benefit is greater in women with incompletely resected (>1 cm residual) stage III and IV disease. The benefit varies over time with maximal benefit in the ICON 7 trial at 12 months and in the GOG 218 trial at 15 months, disappearing by 24 months.146,147 There was no difference in OS in the GOG 218 trial but these data are compromised by postprogression crossover. A 7.8 month median OS benefit was seen in the group of women with incompletely resected (>1 cm residual) stage III and IV disease. The benefit seen in the ICON 7 trial with 7.5 mg/kg for the patients with stage IIIc and >1 cm residual disease or stage IV disease was similar to the benefit seen in the GOG 218 trial with 15 mg/kg suggesting that 7.5 mg/kg is sufficient. The benefit for those with high-risk early disease and stage III disease with residual disease <1 cm was very small.

6.2.6 MAINTENANCE THERAPIES

For advanced ovarian cancer, maintenance cytotoxic chemotherapy should not be given following standard first line chemotherapy. (**LoE: 1++ GoR: A)**

A systematic review including six RCTs of 902 women included a meta-analysis of four RCTs (n=479) of maintenance chemotherapy after complete response to first line platinum and paclitaxel which showed no benefit to overall survival from topotecan, anthracyclines or platinum.154 An additional RCT including 296 women with advanced ovarian cancer who had achieved a complete response to first line platinum-paclitaxel chemotherapy, showed a statistically significant benefit to median PFS of eight months (22 compared with 14 months, p=0.006) but no benefit to overall survival when 12 cycles of maintenance paclitaxel (135 mg/m2, q 21d) compared to three cycles were given following a complete response to primary platinum/paclitaxel (median OS 53 months v 48 months, respectively, p=0.34). There was a higher incidence of grade 2 (23% v 15%) and 3 (6% v 1%) neuropathy, and grade 3 pain (4% v 1%) in the 12-cycle treatment arm.[155] In contrast another study of six cycles of paclitaxel (175mg/m2) after a complete response showed no difference in PFS or OS.[156]

Continued maintenance therapy with bevacizumab following first line carboplatin, paclitaxel and bevacizumab has been shown to delay progression and the use of continued maintenance therapy with other biological agents is under investigation in clinical trials.

1++

154. Mei L, et al. Maintenance chemotherapy for ovarian cancer. Cochrane Database of Systematic Reviews 2010, Issue 9.
155. Markman M, et al. Impact on survival of 12 versus 3 monthly cycles of paclitaxel (175 mg/m2) administered to patients with advanced ovarian cancer who attained a complete response to primary platinum-paclitaxel: follow-up of a Southwest Oncology Group and Gynecologic Oncology Group phase 3 trial. Gynecol Oncol 2009;114(2):195-8.
156. Pecorelli S, et al. Phase III trial of observation versus six courses of paclitaxel in patients with advanced epithelial ovarian cancer in complete response after six courses of paclitaxel/platinum-based chemotherapy: final results of the After-6 protocol 1. J Clin Oncol 2009;27(28):4642-8.

6.2.7 INTRAPERITONEAL CHEMOTHERAPY

Chemotherapy which includes an intraperitoneal element can be considered for women with a new diagnosis of epithelial ovarian cancer and residual disease of ≤1 cm after primary surgery

provided a regimen of proven benefit in a clinical trial compared to intravenous therapy is used, it is delivered in a centre with appropriate expertise and the potential toxicities are fully explained. LoE 1++ GoR: B

A meta-analysis of nine RCTs, including six considered to be of high quality, concluded that women with a new diagnosis of epithelial ovarian cancer (stage II-IV) with residual disease of ≤2 cm, benefited from a chemotherapy regimen that included an intraperitoneal (IP) component compared to intravenous (IV) chemotherapy following primary cytoreductive surgery in terms of survival and progression-free interval (HR=0.81, 95% CI 0.72 to 0.90 and HR=0.78, 95% CI 0.70 to 0.86, respectively).157 Intraperitoneal treatment was associated with greater serious toxicity (grade 3 and 4) with regards to gastrointestinal effects (RR 1.90, 95% CI 1.57 to 2.30), pain (RR 7.47, 95% CI 4.41 to 12.67), fever (RR 1.64, 95% CI 1.13 to 2.38) and infection (RR 3.34, 95% CI 2.06 to 5.43), but less ototoxicity (RR 0.67, 95% CI 0.46 to 0.99), although heterogeneity across trials, probably reflecting differing doses, makes comparison difficult.

However, only three of the trials used an intravenous control regimen that would be considered comparable to current standard IV therapy. […] One trial assessed the effects on quality of life (QoL) and found worse QoL in the IP arm during and immediately after treatment but no difference 12 months after treatment. […]

Wright AA et al., 2016 [14].

SGO, ASCO

Neoadjuvant Chemotherapy for Advanced Ovarian Cancer: Society of Gynecologic Oncology and American Society of Clinical Oncology Clinical Practice Guideline

Leitlinienorganisation/Fragestellung

(3) How do NACT and PCS compare with respect to progression-free survival, overall survival, and perioperative morbidity and mortality in women with newly diagnosed stage IIIC or IV epithelial cancer who are fit for primary cytoreduction and have potentially resectable disease, and how should this information be used to select initial treatment?

(4) What additional clinical evaluations should be performed in all women with suspected or newly diagnosed stage IIIC or IV epithelial ovarian cancer before NACT is delivered?

(5)What is the preferred chemotherapy regimen for women with stage IIIC or IV epithelial ovarian cancer who will receive NACT?

(6) Among women treated with NACT, does the timing of interval cytoreduction or the number of chemotherapy cycles after interval cytoreduction affect the safety or efficacy of treatment?

(7)What are the treatment options for patients with progressive disease on NACT?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Eine regelmäßige Überprüfung war vorgesehen.

Recherche/Suchzeitraum:

- PubMed, the Cochrane Collaboration Library electronic databases published between March 20, 2005, and March 20, 2015

LoE

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

GoR

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (eg, benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases.

Empfehlungen

(3) How do NACT and PCS compare with respect to progression-free survival, overall survival, and perioperative morbidity and mortality in women with newly diagnosed stage IIIC or IV

epithelial ovarian cancer who are fit for primary cytoreduction and have potentially resectable disease, and how should this information be used to select initial treatment?

- Recommendation 3.1—For women who are fit for PCS, with potentially resectable disease, either NACT or PCS may be offered based on data from phase III RCTs that demonstrate that NACT is noninferior to PCS with respect to progression-free and overall survival. NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations, but PCS may offer superior survival in selected patients.
  - Type: evidence based; benefits outweigh harms;
  - evidence quality: intermediate;
  - strength of recommendation: moderate.
- Recommendation 3.2—For women with a high likelihood of achieving a cytoreduction to < 1 cm (ideally to no visible disease) with acceptable morbidity, PCS is recommended over NACT.
  - Type: evidence based; benefits outweigh harms;
  - evidence quality: intermediate;
  - strength of recommendation: moderate.
- Recommendation 3.3—For women who are fit for PCS but are deemed unlikely to have cytoreduction to < 1 cm (ideally to no visible disease) by a gynecologic oncologist, NACT is recommended over PCS. NACT is associated with less peri- and postoperative morbidity and mortality and shorter hospitalizations.
  - Type: evidence based; benefits outweigh harms
  - evidence quality: intermediate
  - strength of recommendation: moderate.

Clinical interpretation: To date, the EORTC and CHORUS studies are the only published randomized phase III trials to compare NACT and PCS. In both studies the median progression-free and overall survival were similar among women who received NACT followed by ICS and those who underwent PCS followed by chemotherapy. However, critics of these trials have noted that both had a shorter median overall survival than what has been reported in previous studies. Prior phase III clinical trials have reported median overall survival times of 45 to 66 months in women who undergo PCS with < 1 cm of residual disease, while the median overall survival was only 32 months and 44 months in patients with < 1 cm residual and no residual disease, respectively, after PCS in the EORTC study. Additionally, some have argued that the "surgical effort" in both EORTC and CHORUS may be lower than the standard of care since the median operative times and rates of upper abdominal surgeries were lower than expected in clinical practice and much lower than what was reported in the SCORPION and JCOG0602 trials.

Alternatively, the lower median overall survival reported in the EORTC and CHORUS trials may reflect the population of patients who were willing to be randomly assigned to a trial comparing PCS and NACT and who had clear evidence of advanced-stage disease based on imaging only. The short survival results may reflect the trial participants, rather than differences in treatment, which included a population of patients who were older, with a poorer performance status, and had higher stage tumors compared with other trials. Observational studies examining women > 65 years of age in the SEER-Medicare database had median survivals that were similar to the EORTC and CHORUS trial participants.37,38 In addition, nearly 25% of the patients enrolled in the CHORUS trial received single-agent carboplatin instead of a platinum-based doublet in both the PCS and neoadjuvant arms. Together, these results suggest that PCS and NACT have similar results in this patient population, but it remains to be seen whether these results apply to populations of patients who are younger, have better performance statuses, or have less bulky disease in light of the data from an exploratory subset analysis of EORTC, which showed that patients with less extensive tumors (≤ 45 mm) had better survival with PCS compared with NACT.6

The extent of residual disease after PCS is a significant prognostic predictor in ovarian cancer reviews.30,39 A recent meta-analysis of studies evaluating survival among patients undergoing PCS for advanced ovarian cancer demonstrated a significant survival advantage associated with patients who had no gross visible disease after surgery; each 10% increase in cytoreduction to no visible disease was associated with a 2.3 month increase in median survival.39 It is unclear whether the extent of residual disease reflects tumor biology, surgical aggressiveness, or both, but PCS to < 1 cm (ideally no visible disease) remains one of the most significant predictors of survival. Therefore, PCS is recommended for those patients with a high likelihood of achieving a cytoreduction to < 1 cm (ideally no visible disease) with acceptable morbidity

(5) What is the preferred chemotherapy regimen for women with stage IIIC or IV epithelial ovarian cancer who will receive NACT?

- Recommendation 5—For NACT, a platinum/taxane doublet is recommended. However, alternate regimens, containing a platinum agent, may be selected based on individual patient factors.
  - type: evidence based; benefits outweigh harms;
  - evidence quality: intermediate;
  - strength of recommendation: moderate.

Treatment of advanced ovarian cancer has evolved over the past decade. Several large phase III studies have demonstrated improved survival with alternate treatment strategies, including IP/IV chemotherapy,31 dose-dense paclitaxel,43 and the addition of bevacizumab for patients with inoperable or sub-optimally cytoreduced disease.44 To date, randomized trials of NACT have tested an every-3-week regimen of IV carboplatin and paclitaxel. […]

At many institutions, patients who receive NACT are not treated with IP/IV chemotherapy after ICS. At present, data on the use of IP/IV chemotherapy after NACT and ICS is limited. A phase II Southwest Oncology Group Study examined the use of IP/IV chemotherapy after NACT and ICS in a group of patients with bulky stage III/IV (pleural effusion only) ovarian cancer for whom optimal cytoreduction was thought to be unlikely on radiographic imaging. Among 58 eligible patients, only 26 patients received NACT, ICS, and postoperative IP/IV chemotherapy; in this group, the median progression free and overall survival were 29 and 34 months, respectively.47 Another ongoing multinational randomized phase II study, PETROC/OV21, is comparing IP/IV carboplatin and paclitaxel versus continued treatment with IV carboplatin and paclitaxel among women who received NACT and optimal ICS.48 This trial was originally designed as a phase II/III clinical trial, but was later modified to a randomized phase II trial due to poor accrual. Nevertheless, in an interim analysis, reported in abstract form, IP/IV chemotherapy was found to be both feasible and safe to use after NACT.49 A comparison of the rates of progression-free survival at 9 months (the new primary end point of the trial) showed 42.2% of women randomized to receive IV chemotherapy had progressive disease, compared with 23.3% of those who received IP/IV chemotherapy.

While these studies suggest that it is feasible and safe to use IP/IV chemotherapy after optimal ICS, there are insufficient data about the efficacy of this approach to make a formal recommendation either for or against the use of IP/IV chemotherapy after NACT at this time.

(6) Among women treated with NACT, does the timing of ICS or the number of chemotherapy cycles after ICS affect the safety or efficacy of treatment?

- Recommendation 6—RCTs tested surgery following three or four cycles of chemotherapy in women who had a response to NACT or stable disease. ICS should be performed after „ 4 cycles of NACT for women with a response to chemotherapy or stable disease. Alternate timing of surgery has not been prospectively evaluated but may be considered based on patient-centered factors.
  - type: informal consensus; benefits outweigh harms;
  - evidence quality: insufficient
  - strength of recommendation: weak.

Patients' responses to NACT should be regularly monitored with clinical assessments and routine measurement of CA-125 each cycle and radiographic imaging should be performed early (preferentially after three cycles of chemotherapy) to assess clinical response. To date, phase III studies have only tested surgery after „ 4 cycles of chemotherapy, and alternate timing has not been prospectively evaluated. Future studies should validate the Chemotherapy Response Score in prospective RCTs, and explore whether it can be used to risk-stratify patients for additional treatment.

(7) What are the treatment options for patients with progressive disease on NACT?

Recommendation 7—Patients with progressive disease on NACT have a poor prognosis. Options include alternative chemotherapy regimens, clinical trials, and/or discontinuation of

active cancer therapy and initiation of end-of-life care. In general, there is little role for surgery and it is not typically advised, unless for palliation (eg, relief of a bowel obstruction).

- Type: evidence based; benefits outweigh harms;
- evidence quality: intermediate;
- strength of recommendation: strong.

Clinical interpretation: Patients who develop progressive disease during neoadjuvant chemotherapy should avoid ICS unless they have a demonstrated response to an alternate chemotherapy. It is very unlikely that an optimal surgical cytoreduction can be achieved in patients with primary platinum-refractory disease, and the survival benefit of a potentially morbid surgery is uncertain in this context. Instead, patients should be offered opportunities to participate in clinical trials, palliative chemotherapy with alternate agents, and/or discontinuation of active cancer therapy and initiation of end-of-life care.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 10 of 12, October 2019) am 16.10.2019

#	Suchfrage
1	[mh "ovarian neoplasms"] OR [mh "fallopian tube neoplasms"] OR [mh "peritoneal neoplasms"]
2	(ovar* OR ("fallopian tube" OR tubal) OR (primary AND peritone*) OR "serous surface papillary"):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions*):ti,ab,kw
4	#2 AND #3
5	{OR #1,#4}
6	#5 with Cochrane Library publication date from Oct 2014 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 16.10.2019

#	Suchfrage
1	ovarian neoplasms/therapy[mh] OR fallopian tube neoplasms/therapy[mh] OR peritoneal neoplasms/therapy[mh]
2	carcinoma, ovarian epithelial[mh]
3	ovar*[tiab] OR fallopian tube[tiab] OR tubal[tiab] OR (primary[tiab] AND peritone*[tiab]) OR serous surface papillary[tiab]
4	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesions*[tiab]
5	(treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab])
6	#3 AND #4 AND #5
7	#1 OR #2 OR #6
8	(#7) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta

	synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation studies[pt] OR validation studies[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
9	((#8) AND ("2014/10/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 16.10.2019

#	**Suchfrage**
1	ovarian neoplasms[mh] OR fallopian tube neoplasms[mh] OR peritoneal neoplasms[mh]
2	ovar*[tiab] OR fallopian tube[tiab] OR tubal[tiab] OR (primary[tiab] AND peritone*[tiab]) OR serous surface papillary[tiab]
3	tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR neoplas*[tiab] OR sarcoma*[tiab] OR cancer*[tiab] OR lesions*[tiab]
4	#2 AND #3
5	#1 OR #4
6	(#5) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
7	((#6) AND ("2014/10/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp])

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